Alternative Interventional/Surgical Methods for the *in-vivo* Thrombogenicity Test

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Traditional Method

- Canines are the preferred animal species (n=2).
- The animals are un-heparinized.
- A percutaneous stick or surgical cut down is performed to gain access to the treatment site.
- Equal lengths of both test and control devices (~10 cm) are inserted into alternating Right and Left Jugular Veins.
- The devices secured to the surrounding tissue to prevent movement.
- The devices are implanted for a total of 4-hours.
- Just prior to euthanasia, a bolus injection of heparin is administered to help prevent post mortem clotting.
- Devices are explanted and evaluated for the presence of thrombus in comparison to the control device.

Traditional Method (Key Concept)

- Reduction in blood flow = Increased probability of thrombus formation.

- Variables that can affect blood flow
  - Treatment site access and securing the device to prevent movement during the 4-hour period.
  - Animal positioning.
  - Location of valves within the treatment sites.
  - Vessel Size and Device Placement.

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Lets Take a Closer Look

- The use of fluoroscopic imaging can help to reduce a number of variables that the current model can overlook.

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Animal Positioning

- The positioning of the animal throughout the study can have a dramatic impact on the blood flow around the device.

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Blood Valves

- Variability in the locations of blood valves can vary from one animal to the next.
- A difference can be seen when comparing right and left jugular veins in the same animal.
- Placement of a device through a blood valve(s) can reduce the blood flow in that particular treatment site.
- This can cause variability amongst the treatment sites.

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Vessel Size and Device Placement

- Size of the vessel in relation to the device can have a impact on thrombus formation.
- The size and shape of the device should be considered prior to deployment.
- Patency and proper deployment of the device must be evaluated immediately post implant with the use of fluoroscopy.
- If the Device is in contact with the vessel wall during the 4-hour indwelling period, there is a higher probability of thrombus formation.

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Consider using both the Jugular and Iliac veins

- The Iliac veins provide another treatment site for both test and control device.
- The Iliac veins have adequate blood flow while the animal is on the table.
- This design allows for an evaluation of one additional test and control device in each animal on study.
- This helps to reduce the potential of receiving conflicting results.

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Jugular and Iliac Method Considerations

- There are many procedural related variables that can affect blood flow.
- The use of fluoroscopic imaging can help to reduce these variables.
- Vessel size should be evaluated prior to implantation.
  * As a general rule, any device larger than 10 Fr should be evaluated in a sheep.
- Proper evaluation of the device deployment and patency should be evaluated with the use of angiography.
- This method should considered for the evaluation of devices such as dilators, sheaths, guidewires and standard catheters.

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Swine Atrial Model (surgical approach)

- Two swine are subjected to bilateral atrial implants.
- A sternotomy is performed, a sheath is placed, and the test and control devices are deployed into the right and left atrium.
- The use of contrast and fluoroscopic imaging must be used to ensure the proper deployment of the devices prior to removing the sheaths.
- This design can be used without Heparin.

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Considerations for the Swine Atrial Model

- This devices can be implanted without the use of Heparin.
- Device Recommendation: Balloon Catheters, Mapping Catheters and Larger devices.

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Interventional Thrombogenicity Test

- Canine, Sheep or Swine can be used.
- Clinical relevance (intended implant location, venous verses arterial blood flow), vessel size, blood flow, size and shape of the device should be considered with the design.
- A surgical cut down or percutaneous stick may be used to gain access to the vascular system (example: femoral vein access)
- Heparin is administered to maintain an Activated Clotting Time (ACT) level > 250 seconds during the device placement procedure.

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Interventional Thrombogenicity Test

- Devices are deployed under fluoroscopic guidance.
- Fluoroscopic images are obtained with the use of contrast to ensure proper placement and blood flow around the device.
- ACT's are taken until the animal approaches baseline and then the four hour indwelling period begins.
- I will give a few examples of recommended deployment sites, but this design is very robust, minimally invasive, and the model is completely customizable to the device.

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Interventional Thrombogenicity Test

- By far the best design.
- Minimally invasive.
- Devices are deployed under fluoroscopic guidance.
- Fluoroscopic images are obtained with the use of contrast to ensure proper placement and blood flow around the device.
- The design is customized to the device.

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Thrombus Evaluation

- Take Pictures!!!

Thrombus Evaluation Scores

Device Thrombus Formation Score	Descriptions
0	Minimal to nonexistent formation (1% or less)
1	Minimal – Observed to be covering 2 to 10% of material length
2	Mild – Observed to be covering 11 to 25% of material length
3	Moderate – Observed to be covering 26-50% of material length
4	Extensive – Observed to be covering 51-75% of material length
5	Severe – Observed to be covering > 75% of material length
Vessel Thrombus Formation Score	**Descriptions**
0	Minimal to non-existent occlusion (1% or less)
1	Minimal – Vessel observed to be 2 to 10% occluded by thrombus
2	Mild – Vessel observed to be 11 to 25% occluded by thrombus
3	Moderate – Vessel observed to be 26-50% occluded by thrombus
4	Extensive – Vessel observed to be 51-75% occluded by thrombus
5	Severe – Vessel observed to be >75% occluded by thrombus

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Interpretation of the Results

Test Score of the Device	Comparison to the control	Evaluation
0-1	NA	Non-Thrombogenic
2	Equivalent	Non-Thrombogenic
2	Not Equivalent	Further evaluation required
3 or higher	Equivalent	*Suspected Thrombogenic further evaluation required
3 or higher	Not Equivalent (Control Score is 2 or less)	Thrombogenic

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Thank You!!!

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